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09/671,687	09/28/2000	David Wallach	WALLACH=25	7238

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EXAMINER	
SCHLAPKOHL, WALTER	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/671,687	WALLACH ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,20-24,38,40 and 42-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *44-46* is/are allowed.

6)☒ Claim(s) *2,3,20-24,38,40,42,43 and 47-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/646,403.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of papers filed 2/22/2007 in which claims 2, 21, 38 and 42-44 were amended and claims 49-50 were added. Claims 2-3, 20-24, 38, 40 and 42-50 are pending and under examination in the instant Office action.

Claim Objections

The objection to claims 42 and 43 as being essentially duplicates of claims 39 and 40, respectively, is hereby WITHDRAWN in view of Applicant's cancellation of claim 39 and in view of Applicant's amendment to claim 43.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 42, 43 & 49, and therefore dependent claims 3, 20-24, 38, 40, 47-48 & 50, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which Applicant regards as the invention. **These are new rejections necessitated by Applicant's amendment.**

Claim 2 recites "[a]n isolated protein which is capable of binding to tumor necrosis factor receptor-associated 2 protein (TRAF2), said protein comprising:

(A) a polypeptide consisting of the amino acid sequence of SEQ ID NO:3; or

(B) a variant consisting of an amino acid sequence that is at least 90% identical with SEQ ID NO:3, wherein said variant is capable of binding to TRAF2" in lines 1-10 (emphasis added). Claim 2 is vague and indefinite in that it is unclear whether Applicant intends a TRAF2 binding protein from the group comprising a polypeptide which consists of either SEQ ID NO:3 and variant of SEQ ID NO:3 wherein the variant is at least 90% identical to SEQ ID NO:3; or whether Applicant intends a TRAF2 binding protein comprising SEQ ID NO:3 or a variant of SEQ ID NO:3, wherein the variant is at least 90% identical to SEQ ID NO:3.

Claim 42 recites "[a]n isolated protein in accordance with claim 2, comprising a variant of the polypeptide consisting of the amino acid sequence of SEQ ID NO:3, which variant consists of an amino acid sequence that is at least 90% identical with SEQ ID NO:3, and which variant is capable of binding to TRAF2"

in lines 1-6 (emphasis added). Claim 42 is vague and indefinite in that it is unclear whether Applicant intends a variant comprising any from the group which *consists* of amino acid sequences that are limited to those with at least 90% identity to SEQ ID NO:3 and which bind to TRAF2, or whether Applicant intends any polypeptide comprising a variant of SEQ ID NO:3 with 90% identity to SEQ ID NO:3.

Similarly, claim 43 recites "an isolated protein …comprising a variant of the polypeptide consisting of…SEQ ID NO:3, which variant consists of an amino acid sequence that is at least 95% identical with SEQ ID NO:3…" in lines 1-6. Claim 43 is vague and indefinite as explained for claim 42, above.

Claim 49 recites "[t]he isolated protein of claim 47, wherein each said change from the amino acid sequence of SEQ ID NO:3 is…a conservative substitution that is an exchange within one of the following five groups:

Small aliphatic, nonpolar or
slightly polar residues: Ala, Ser, Thr (Pro, Gly);

Polar negatively charged
Residues and their amides: Asp, Asn, Glu, Gln;

Polar, positively charged residues: His, Arg, Lys;

Large aliphatic nonpolar

residues: Met, Leu, Ile, Val (Cys);

and

Large aromatic residues: Phe, Tyr, Trp" (emphasis added). Claim 49 is also vague and indefinite in that the use of parentheses with regard to Pro, Gly, and Cys residues is unclear. For example, does Applicant intend to distinguish amino acids in parentheses as provisional or conditional substitute residues; or, because these particular amino acids represent structurally significant residues, does Applicant intend e.g., to indicate that these residues are distinguished by their structural properties within a protein sequence?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 20-24, 38 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the

written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record but has been slightly altered in order to accommodate Applicant's amendment.**

Response to Arguments

Applicant argues that all of the rejected claims make clear that the variant of SEQ ID NO:3 must bind to TRAF2, and therefore that the claims include a functional limitation. Furthermore, Applicant argues that paragraph (B) of claim 2 states that the amino acid sequence of the variant is the same as the defined amino acid sequence of SEQ ID NO:3 except for changes to the sequence thereof that still leave at least 90% identity (claim 2) or 95% identity (claims 40 and 43), or that have only ten changes (claim 47) or only five changes (claim 48), or ten or five changes that are conservative changes (claims 49 and 50). Therefore, Applicant argues, the claims further define the sequences by structure. Applicant asserts that "this combination of partial structure and physical and/or chemical properties is sufficient to show that applicant was in

possession of the claimed invention" (see page 10, lines 4-7 of the Remarks filed 2/22/2007).

Applicant further argues that the Revised Interim Written Description Guidelines Training Materials teach at Example 14 a situation wherein a protein having hypothetical SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and which catalyze the reaction of A→B are claimed. Example 14 further indicates that the specification corresponding to hypothetical protein of SEQ ID NO:3 contemplates, but does not identify, variants with substitutions, deletions, insertions and additions, and further that the specification provides an assay for detecting the catalytic activity of the protein. Applicant further argues that the instant Application's specification also contemplates variants with 95% identity to the instant SEQ ID NO:3 and that the instant specification also discloses a functional assay which provides for the identification of 95% identical variants with the required TRAF2 binding function.

Applicant further argues that while Example 14 of the Training Materials specifically relates to an example with 95% identity, the logic therein equally applies to variants with 90% identity because the analysis is the same.

Applicant's arguments have been carefully considered and have been found persuasive IN PART. Specifically, Applicant's

arguments with respect to variants with 95% or greater identity to SEQ ID NO:3 are found persuasive. However, Applicant's argument with respect to the variants with 90% identity to SEQ ID NO:3 (i.e., less that 95% identity to SEQ ID NO:3) are not found persuasive because 1) the degree of variation is no longer appropriately analogous to Example 14 of the Training Materials and 2) the size of the genus encompassed by variants with as little as 90% identity is too large for SEQ ID NO:3 to be representative of the entire class of variants encompassed by the claim. Thus, even armed with a functional assay for identification of proteins encompassed within the claimed genus of SEQ ID NO:3 variants, the limited number of disclosed species in the specification is not representative of the significantly larger genus of variants encompassed by those with only 90% (as opposed to 95%) identity to SEQ ID NO:3.

Claims 2, 20-24, 38, 40 and 42-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record**

but has been slightly altered in order to accommodate Applicant's amendment.

Response to Arguments

Applicant argues that claim 2 has now been amended in order to clarify the scope of the invention, i.e., the protein comprises either an amino acid sequence consisting of SEQ ID NO:3 or a variant consisting of an amino acid sequence that is at least 90% identical with SEQ ID NO:3, wherein the variant is capable of binding to TRAF2. With regard to the amount of experimentation required, Applicant argues that while "the quantity of experimentation may be significant, as random mutations would have to be generated and screening conducted of the encoded proteins using a simple binding assay…in the *Wands* case, it was found that routine screening does not necessarily amount to undue experimentation" (see paragraph bridging pages 17-18 of the Remarks filed 2/22/2007). Applicant further argues that binding assays do not involve undue experimentation. With respect to the amount of guidance or direction presented, Applicant argues that "the specification refers at pages 31 and 39 to the Sambrook reference, which is the laboratory manual used by everyone of ordinary skill in this art" (page 18, 1st full paragraph of the Remarks filed 2/22/2007). With regard to

the presence of working examples, Applicant argues that the binding assay at page 19 is sufficiently detailed to serve as a working example. With regard to the nature of the invention, Applicant argues that the nature of the invention is such that substantial experimentation is acceptable and that those of ordinary skill in the art are "inured to screening that takes substantial experimentation quantitatively" (see page 18, last paragraph of the Remarks filed 2/22/2007). With regard to the state of the prior art, Applicant argues that random mutagenesis and binding assays are well known in the art and that simple binding assays can be done in a high throughput manner. With regard to the relative skill of those in the art, Applicant argues that those or ordinary skill in the art of recombinant DNA technology is very high, usually requiring a Ph.D. and/or substantial laboratory experience, and that for such persons a greater amount of experimentation would be considered to be routine than for technologies requiring a lower level of skill in the art. With regard to the predictability of the art, Applicant argues that unpredictability with regard to sequence and structural requirements necessary to bind to TRAF2 fail in view of the fact that it is not necessary to know in advance which variants of SEQ ID NO:3 would bind to TRAF2. Applicant further argues that predictability is "not relevant here" as one

need only do the experiments and screen. With regard to the breadth of the claims, Applicant argues that paragraph (B) of claim 2 is not so broad so as to require undue experimentation to find what would fall within it for the reasons as discussed above. With regard to Examiner's assertion that the claims could read on a protein in which the N-terminal 94 residues are completely different from those of SEQ ID NO:3, which sequence could represent an independently functional domain, Applicant argues that this is a "far-fetched" argument. Applicant further argues that Examiner has not met his burden of suggesting any 94 amino acid sequence that would be known to bind to TRAF2 and that does not appear in SEQ ID NO:3. Applicant further asserts that in the instant case, identification of the protein and making the invention *are* synonymous, because "any variant that binds to TRAF2 is the present invention" (see page 21, 1st paragraph of the Remarks filed 2/22/2007).

Applicant's arguments have been carefully considered but have respectfully been found unpersuasive. To begin, Applicant's amendment of the claim 2 has not clarified the scope of the invention. Indeed, the scope of the claim was clearer prior to Applicant's amendment (see the rejection of claim 2 under 35 USC 112, 2nd paragraph, above).

Applicant's argument that while "the quantity of experimentation may be significant...in the *Wands* case, it was found that routine screening does not necessarily amount to undue experimentation" and that binding assays do not constitute undue experimentation, is not persuasive because, as Applicant concedes, the quantity of experimentation is significant and because the quantity of experimentation is indeed undue. As has been previously explained, whether or not mutation techniques and binding assays are "routine" in the art, Applicant's invention is an invitation to identify that which is the Applicant's invention. Without any guidance with regard to the domains of the protein which are functional for binding, one of ordinary skill in the art is required to guess which amino acids from among the 949 of SEQ ID NO:3 are necessary for the protein's claimed function. Without a frame of reference for where to begin (guidance provided by the prior art and/or the specification), such binding and mutation assays are no longer "routine" but in fact burdensome and undue. With regard to the amount of guidance provided by the specification, Applicant's argument that the specification refers to Sambrook et al is not persuasive because 1) Applicant has not claimed a method which can be performed according to Sambrook, and 2) Sambrook does not teach protein variants of SEQ ID NO:3 which do or do not bind to

TRAF2, or protein domains thereof. Applicant's argument that unpredictability with regard to sequence and structural requirements necessary to bind to TRAF2 fail in view of the fact that it is not necessary to know in advance which variants of SEQ ID NO:3 would bind to TRAF2 is not persuasive because it is predicated upon Applicant's assertion that as long as one can identify Applicant's invention using mutagenesis techniques, binding assays, and homology to SEQ ID NO:3, the invention is enabled. However, as has already been explained, that is not the case when such assays would comprise a burdensome and undue amount of experimentation. Applicant's argument that predictability is "not relevant here" as one "need only do the experiments and screen" is also not persuasive because of those reasons already cited and because predictability is indeed relevant in any consideration of whether or not Applicant has enabled one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the claimed invention. Examiner also finds Applicant's argument with regard to the binding assay at page 19 as sufficiently detailed to serve as a working example unpersuasive, because a binding assay is not the claimed invention; the claimed subject matter is drawn to variants of SEQ ID NO:3 with 90% or greater identity to SEQ ID NO:3 capable of binding to TRAF2.

Applicant's argument that the nature of the invention is such that substantial experimentation is acceptable and that those of ordinary skill in the art are "inured to screening that takes substantial experimentation quantitatively" is not found persuasive because Applicant's argument is again predicated upon the notion that 1) a large amount of routine experimentation would not be undue if the techniques involved are routine; and 2) that those of ordinary skill in the art are "inured" to a large quantity of experimentation and as such would not find the work burdensome or undue. As has already been explained, the use of routine procedures does not necessarily result in a lack of burden with regard to experimentation when, for lack of guidance and disclosure in the specification and the prior art, one of ordinary skill in the art would not know where to begin performing such assays and, indeed, would instead have to resort to trial and error experimentation in order to identify embodiments encompassed within the full scope of Applicant's claims. Furthermore, although Examiner agrees with Applicant insofar as the level of skill in the art of recombinant DNA technology is very high, Examiner disagrees with Applicant in that a greater amount of experimentation for such persons would be considered to be routine than for technologies requiring a lower level of skill in the art. In this Applicant appears to

be comparing apples and oranges; other technologies would have a different standard altogether for the level of skill of one of ordinary skill in the art, and thus the amount of experimentation which is considered burdensome and/or undue would therefore be based on the skill level appropriate for that art. Finally, Examiner's assertion that the claims read on a protein in which the N-terminal 94 residues are completely different from those of SEQ ID NO:3, is not "far-fetched" as described by Applicant. Indeed, based on Applicant's concession that such a protein is "far-fetched," it would seem clear that the breadth of Applicant's claims does indeed encompass embodiments which were not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Allowable Subject Matter

Claims 44-46 are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is

reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Joseph Woitach can be reached at (571) 272-0739.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

April 27, 2007

DAVID GUZO
PRIMARY EXAMINER